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Short Communication

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Evolving Approach and Current Perspectives of Gallbladder Polyps and Adenomyomatosis

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Abstract

The gallbladder is commonly examined for incidental findings. Since gallbladder malignancy has a poor prognosis, distinguishing benign from malignant lesions is crucial. Radiologists and sonographers should therefore be aware of common gallbladder incidental findings, which will undoubtedly increase with increasing medical imaging use. Gallbladder and biliary tree imaging is primarily performed by ultrasound, but contrast-enhanced ultrasound (CEUS) and magnetic resonance imaging (MRI) are becoming more common. It discusses two common gallbladder incidental findings, adenomyomatosis and gallbladder polyps. We will review and compare the imaging features of these conditions between radiological modalities, and discuss the pathology, epidemiology, natural history, and management of these conditions.

Introduction

Gallbladder diseases are on the rise worldwide. Annually, there are more than 200,000 cases of gallbladder and biliary tract cancer, but incidental findings such as polyps and adenomyomatosis are far more common. It is the most common malignancy of the biliary tree, but there are only approximately 1,100 cases per year in the United Kingdom. In addition to being aware of incidental gallbladder findings, clinicians, and particularly radiologists, need to be knowledgeable about them, as detection continues to increase [1]. Gallbladder polyps and adenomyomatosis are the two most common incidental gallbladder findings reviewed in this article. These common incidental gallbladder findings are reviewed in terms of their imaging features on different radiological modalities, as well as their epidemiology, natural history, and management [2].

Methods

For the purpose of this review, a detailed literature review was conducted. We searched MEDLINE using combinations of terms 'gallbladder', 'polyps', and 'adenomyomatosis', without any restriction on language or date.

Gallbladder polyps

Background

Transabdominal ultrasound (TAUS) frequently detects gallbladder polyps, which are increasingly prevalent as the use of medical imaging increases [3]. A gallbladder polyp is defined as an elevation of the mucosal surface of the gallbladder that protrudes into the gallbladder lumen and that does not move or show posterior acoustic shadowing on TAUS imaging. There are two types of gallbladder polyps: true polyps and pseudo polyps [4]. The former are sessile polyps, while

the latter are pedunculated polyps. The most common type of true polyp is the gallbladder wall adenomas, which are thought to have malignant potential. In addition to fibromas, lipomas, and leiomyomas, gallbladder polypoids can also be malignant, such as mesenchymal neoplasms, lymphomas, and metastases, although these are far more rare than common adenomas [5]. A pseudo polyp does not have malignant potential and is commonly an inflammatory polyp, an adenomatous polyp, or a cholesterol foci. Gallbladder pseudo polyps are believed to account for at least 70% of all polyps detected by TAUS. Also included in false-positive findings are impacted calculi attached to the gallbladder wall, echogenic sludge, and mucosal folds. The presence of gallbladder polyps is usually incidental since they are typically asymptomatic. Gallbladder polyps may cause intermittent pain, nausea and vomiting in the right upper quadrant when symptoms are present [6].

Epidemiology

In adults, gallbladder polyps are estimated to occur in 0.3 - 12.3% of cases. There is a male predilection for gallbladder polyps and a median age at diagnosis ranging from 40 to 58 years. Raised body mass index is associated with a greater prevalence of cholesterol polyps. Although gallbladder polyps are mostly associated with adults, they can also develop in children, however, this review article does not address this issue [7]. The incidence of gallbladder cancer is relatively uncommon, despite the prevalence of gallbladder polyps. Just 20% of gallbladder cancer patients survive five years or longer, a poor prognosis. In order to detect gallbladder cancer at an early stage, it is vital to distinguish benign findings from malignant ones (Figure 1) [8].

Figure 1: Incidence of gallbladder cancer worldwide [9].

Natural history

Adenoma-carcinoma progression from gallbladder polyps to cancer remains controversial. The sequence of adenoma-carcinoma in gallbladder polyps has been studied. However, a study by Kai et al found that adenomas did not exhibit the molecular changes associated with dysplasia, carcinoma *in situ*, and invasive malignancy, indicating that adenomas may not be precursors to gallbladder cancer [10].

A few high-quality studies have estimated the absolute risk of gallbladder polyp malignancy, but this data suggests the risk is very low. There were 11.3 gallbladder cancers per 100,000 person/year's according to a large North American study including over 600,000 patients with gallbladder polyps (95% confidence intervals (CI) 6.2 - 16.3). Cancer rates increased with polyp size, from 1.3 (95% CI 0.7 - 6.5) in polyps less than 6 mm, to 128.2 (95% CI 9.4 - 217.0) in polyps greater than 10 mm. For polyps smaller than 10 mm, the authors hypothesized that 95,624 ultrasound examinations would be required after the first year to detect one gallbladder cancer (corresponding to a rate of 1.05 per 100,000 scans). A 20-year study also showed that gallbladder polyps naturally grow slowly, raising concerns about the current strategy of monitoring polyps based on their size [11, 12].

Risk factors for malignancy

The following clinical factors have been associated with a higher risk of malignancy in patients with gallbladder polyps [13].

Polyp size

There is an established association between gallbladder polyp size and the risk of malignancy, but the risk remains relatively low even when polyps measure 10 mm or larger. Size is often used as a criterion for guiding the management of patients in many international guidelines. Malignant polyps typically exceed 10 mm in size. As of diagnosis, 75% of gallbladder adenocarcinomas measured more than 10 mm. The risk of gallbladder cancer is rare for polyps less than 10 mm in size [14].

Primary sclerosing cholangitis (PSC)

Coexistence of PSC and gallbladder polyps is associated with a higher risk for malignancy. Gallbladder polyps are more common than in the general population, according to several small, retrospective observational studies and have an increased risk of malignancy [15]. Four hundred and fifty-three patients with PSC were studied by Yoon et al. [16] across two centres, and 16% had gallbladder polyps. There were 8.8 gallbladder cancers per 1000 person-years (CI 1.8 - 25.7). Of 18 patients with polyps, 56% had malignancy. It seems that even small polyps less than 10 mm are associated with an increased risk of malignancy [16].

Patient age

In addition to patient age, there are several confounding factors associated with gallbladder cancer from polyps. Also, age is a common criterion for guiding management, but the threshold for recommendations remains unclear. Each of the following age-appropriate thresholds for malignant risk has been proposed: 50 years, 60 years, and 65 years [17].

Number of polyps

A systematic review and multicentre series have demonstrated an increased risk of malignancy for solitary polyps, suggesting that solitary polyps should be considered with other known clinical risk factors. Other retrospective and single-center studies have concluded that a single polyp is an independent risk factor for malignancy, however, details concerning confounding factors are often missing [18].

Sessile morphology

An eccentric gallbladder wall thickening, and a sessile polyp can be difficult to distinguish on imaging. Accordingly, these two factors are often grouped together in guidelines. According to a systematic review by previous authors, sessile morphology was an independent risk factor for gallbladder cancer (odds ratio 7.32; 95% CI 4.18 - 12.82). A study by Yoshimitsu et al. [19] found similar results. Other retrospective studies have shown a link between gallbladder wall thickening and malignancy [19]. These studies are of low quality given their design and sample sizes, so there is limited evidence for sessile morphology to be a risk factor for malignancy. An ultrasound-based risk stratification system for gallbladder wall thickening has been proposed, but the clinical validity and utility of this system have yet to be published [20].

Ethnicity

Malignancies are rarely associated with ethnicity. It was demonstrated by previous authors that Indian ethnicity increases cancer risk. Further, Joo et al. [21] discovered that East Asian populations had a higher incidence of malignant gallbladder polyps [21].

Gallstones

The presence of gallstones as a risk factor for malignancy has been described, but with varying evidence. One study suggested that gallstones may mechanically disrupt the formation of gallbladder polyps when present in the gallbladder [22]. Gallstones are not included in international guidance because the evidence is not conclusive.

Radiological investigation of gallbladder polyps

Gallbladder polyps are routinely detected, diagnosed, and monitored using TAUS. However, in certain circumstances with appropriate expertise, other imaging modalities may be considered as an aid to decision-making (Figure 2) [23].

Figure 2: Polyp inside gall bladder [24].

Imaging features

Radiological modalities as well as the underlying polypoidal pathology affect imaging features of gallbladder polyps. There are, however, overlaps in imaging features, which can make differentiating gallbladder polypoid lesions difficult. An overview of the imaging characteristics of commonly occurring incidental gallbladder lesions can be found, while a comparison of benign and malignant imaging characteristics can be found.

It is probably most important to distinguish between benign and malignant gallbladder lesions. On several imaging modalities, gallbladder cancer commonly appears as a large, heterogeneous mass. It can also occur as thickened gallbladder walls or polypoid lesions. Malignancy is highly suggestive of an infiltrating mass into adjacent structures. An ultrasound scan of an adenocarcinoma shows a nodular surface, round shape, and heterogeneous internal echo. Demonstration of internal vascularity is associated with adenocarcinoma but can also be seen in adenoma.

Gallbladder metastases are uncommon, but possible. There are primary malignancies, including malignant melanoma, renal cell, gastric, hepatocellular, and lung carcinomas. The imaging characteristics of gallbladder metastases include focal wall thickening and increased vascularity. If there is a history of malignancy, metastases should be suspected [25].

TAUS

There are hyperechoic adenomas compared to nearby bile, and they are immobile. It is possible for adenomas to be sessile or pedunculated, and they lack posterior acoustic shadowing. Pedunculated polyps often do not have a stalk visible. Doppler imaging can reveal internal vascularity in adenomas, which vary in size.

The appearance of pseudopolyps, however, varies depending on their constitution. An ultrasound feature of a pseudo polyp is reverberation or the comet tail artefact posterior to a polypoid lesion. An acoustic shadow may appear behind cholesterol polyps when they are pedunculated, solitary, or multiple. They are usually smaller than 10 mm, may have a granular surface or a tiny spotted echo pattern inside, and have a homogeneous or a granular surface. In the presence of doppler flow, cholesterol polyps may exhibit a "twinkling artefact". Despite their variability in imaging features, pseudopolyps are difficult to distinguish from true polyps. Pseudopolyps caused by inflammation are less common and associated with chronic cholecystitis. A sessile or pedunculated seed is usually smaller, homogenous, and sessile [2].

Polypoid gallbladder lesions are reasonably detectable with TAUS. In a systematic review by Xie et al. [26] six studies (16,260 participants) investigated TAUS. According to the results of the study, TAUS is 84% (95% CI 59 - 95%) sensitive and 96% (95% CI 92 - 98%) specific for gallbladder polyp detection. Gallbladder polyps can be diagnosed and followed up with TAUS due to its high sensitivity and specificity. In recent studies, however, it has been shown that TAUS often detects polyps that are not true. The false-positive rate for TAUS has been reported as high as 85% in one systematic review. Pathology confirmed pseudopolyps (59%) and cholelithiasis (38%). The low positive predictive value may result in unnecessary monitoring and cholecystectomy. A similar reduction in diagnostic accuracy occurs when TAUS is used to distinguish between polyps and pseudopolyps. There was a 68% summary sensitivity (95% CI 44 - 85%) and a 79% summary specificity (95% CI 57 - 91%). A large proportion of gallbladder polyps may be monitored inappropriately based on these data, as well as estimates that around 70% are pseudopolyps [26].

The tumefactive biliary sludge and gallstones mimic polypoid gallbladder lesions. A tumefactive biliary sludge is characterized by adhesion to the gallbladder wall and is thus non-mobile. Simple biliary sludge often appears as layers, is hyperechoic, lacks posterior acoustic shadowing, and is mobile. Despite its lack of internal vascularity, tumefactive biliary sludge can exhibit twinkling artifacts on doppler assessment due to cholesterol deposits or calcifications. When gallstones are located in the neck of the gallbladder or are mobile, hyperechoic, and have posterior acoustic shadowing, they are difficult to visualize.

High-resolution ultrasound (HRUS)

TAUS transducers that operate at a high frequency (at least 10 MHz) have better resolution, but less penetration than transducers that operate at a low frequency. Compared with low frequency transducers, high frequency transducers allow for a more accurate assessment of polyp internal echoes and a better visualisation of gallbladder walls. As an adjunct to TAUS, HRUS is being investigated for the assessment of gallbladder polyps. The HRUS of neoplastic polyps revealed a single lobular surface, a vascular core, hypo echogenicity, and internal hypoechoic foci [27].

CEUS

TAUS can also be supplemented with CEUS. With CEUS, it is possible to determine whether a polypoid lesion is benign or neoplastic and to distinguish non-vascular from vascular components. A CEUS can also be used to visualize polyp contours, morphology, size, and margins. A study by Yoshimitsu et al. [28] found CEUS to be more accurate than TAUS at diagnosing diseases. There was a 94.1% sensitivity and 95.5% specificity difference between CEUS and TAUS in distinguishing benign from malignant polypoid gallbladder lesions. The arterial phase of adenomas usually increases homogeneously, and the venous phase becomes isoechoic, whereas the venous phase of adenocarcinomas decreases homogeneously. As a result, pseudopolyps and sludge should not enhance [28].

Endoscopic ultrasound (EUS)

By performing an EUS, close contact can be made with the gallbladder, which produces higher-resolution images. The EUS allows the visualization of the mucosa, muscularis propria, and subserosa of the gallbladder wall, as well as the assessment of the morphology and surface of gallbladder polyps [29]. Due to a lack of routine use of EUS for gallbladder polyps, limited diagnostic accuracy data exists for EUS over TAUS. Compared to TAUS, EUS differentiates true polyps from pseudopolyps more accurately. EUS has a summary sensitivity of 85% (95% CI 46 - 97%), and a summary specificity of 90% (95% CI 78 - 96%), compared to TAUS which has a summary sensitivity of 68% (95% CI 44 - 85%) and 79% (95% CI 57 - 91%). The authors concluded that there was no significant difference in diagnostic accuracy between TAUS and EUS when detecting true polyps and pseudopolyps.

Computed tomography (CT)

Gallbladder polyps cannot be diagnosed or staged with CT in clinical practice, but rather are diagnosed, or staged, using CT. In addition to providing extra biliary information, CT has become increasingly accessible. In a study by Haradome et al. [30] TAUS detected gallbladder polyps more sensitively than CT. A retrospective, single-center study found the presence of polyps only 63% of the time on CT, whereas only 45% of polyps smaller than 13 mm were visible on CT. A retrospective, single-center study found the presence of polyps only 63% of the time on CT. CT imaging features can assist in distinguishing non-neoplastic polyps from neoplastic polyps. The presence of irregular margins and sessile shape are indicators of neoplastic polyps. The larger the polyp (> 15 mm), the more likely it is to be neoplastic [30]. Furthermore, contrast enhancement on CT has been reported to predict malignancy. In a retrospective study, by previous authors found that gallbladder polyps with hyperenhancement of 1 - 2 cm were more likely to be cancerous.

MRI

An increasing number of gallbladder and biliary tree procedures use MRI as an imaging adjunct and problem-solving tool. The MRI signal for 57 gallbladder adenomas is generally homogeneous. DWI was compared with three morphological features (mass, disrupted mucosa line, and two-layered pattern absence) in a retrospective, single-center study by Ogawa et al. It had a sensitivity of 76.9%, a specificity of 84.0%, and an accuracy of 83.0% when two or more morphological features suggested malignancy. A combination of morphological features and apparent diffusion coefficient values led to 73.0% sensitivity, 96.2% specificity and 92.9% accuracy. Tumefactive sludge will not demonstrate diffusion restriction and have high T1 signal 45 compared to gallbladder malignancy [31].

Positron emission tomography (PET)

PET can also distinguish benign and malignant gallbladder wall thickenings that may be present incidentally on this imaging modality. In a small study by previous authors, the mean standardized uptake value (SUV_{max}) of malignant thickening was significantly higher than that of benign thickening (SUV_{max} 4.5). SUV_{max} cut-off of 5.95 demonstrated 92 and 79% sensitivity and specificity for detecting malignancy.

Management of gallbladder polyps

Clinical guidelines for managing gallbladder polyps have been developed by several international societies and organizations. Treatment options and follow-up frequency and duration are usually guided by clinical and size-based criteria. Despite a lack of prospective or randomized data, management recommendations for gallbladder polyps are based on the evidence base. It is still unclear whether monitoring gallbladder polyps, especially small polyps, is beneficial, and whether management strategies are clinically and cost-effective. There was no significant difference in gallbladder cancer rates between patients with and without polyps on ultrasound examinations

in a large North American study by Szpakowski and Tucker (0.053% and 0.054%). Joint European societies updated their guidelines for managing gallbladder polyps in 2021. When patients are fit for surgery and have polyps measuring 10 mm or more, or if they have gallbladder-related symptoms, cholecystectomy is still recommended. In cases of polypoid lesions that are less than 10 mm in diameter, clinical risk factors should be considered. A sessile lesion and age over 60 are clinical risk factors. When a polyp measure 6 - 9 mm and there are clinical risk factors, a cholecystectomy is recommended. Additionally, a solitary polyp is a risk factor for malignancy, which should be considered alongside cholecystectomy. It depends on the size and presence of risk factors whether ultrasound monitoring should be conducted frequently or for a prolonged period of time. If the polyp measures no more than 5 mm and there are no risk factors, the patient no longer needs follow-up [32].

Adenomyomatosis

Background

There is a condition known as adenomyomatosis, which is characterized by thickening of the gallbladder wall, which is benign and noninflammatory. In adenomyomatosis, the epithelial cells of the gallbladder multiply and hypertrophy, resulting in mucosal outpouching into the thickened muscular wall. It is called Rokitansky-Aschoff sinuses, which contain bile, which dehydrates and inspissates over time, causing cholesterol crystals to precipitate. Chronic inflammation may lead to dystrophic calcification as a result of the crystals.

In adenomyomatosis, the gallbladder wall thickens in three main ways: focal, segmental, and diffuse [33]. Adenomyomatosis of the fundus is the most common pattern. There can be challenges in distinguishing between adenomyomatosis and malignancy in focal adenomyomatosis. An annular or segmental adenomyomatosis manifests as a limited circumferential thickening of the gallbladder wall. An hourglass-shaped appearance is caused by segmental adenomyomatosis of the gallbladder. Generally, diffuse adenomyomatosis thickens the gallbladder wall.

Epidemiology

The incidence of adenomyomatosis in adult cholecystectomy specimens is estimated at 2.0 - 8.7%. The prevalence of adenomyomatosis is higher in females than in males. There has been some evidence that adenomyomatosis occurs in children, but it is rare. Biliary colic symptoms may occur with adenomyomatosis, although gallstones can be a confounding factor. Approximately 50% of fundamental and diffuse adenomyomatosis cases have gallstones, while segmental cases can have up to 90% [34].

Natural history

Adenomyomatosis is considered benign, even though dysplastic changes and carcinomas have been reported from segmental adenomyomatosis. Patients with adenomyomatosis have a high risk of developing cholelithiasis, and the tumor can grow naturally as it progresses [35]. The size of the tumor does not increase with malignancy, which is an important finding.

Imaging features of adenomyomatosis

The reader can make a confident diagnosis of adenomyomatosis based on certain classical features. Radiologists must keep in mind, however, that gallbladder polyps can overlap with malignancies. Symptoms of adenomyomatosis, such as gallbladder masses, can make assessment difficult [36]. It is recommended to consider early cholecystectomy if the underlying diagnosis is uncertain.

TAUS

In addition to TAUS, MRI offers complementary imaging features that enhance diagnostic accuracy in adenomyomatosis. Anechoic cystic spaces 42 are seen within the gallbladder wall in adenomyomatosis. There may be echogenic foci, comet tail reverberation artefacts, acoustic shadowing, or twinkling artefacts resulting from Rokitansky-Aschoff sinuses filled with cholesterol crystals, biliary sludge, or calculi.

CT

Rokitansky-Aschoff sinuses are what is described as a "rosary sign" in CT. The rosary sign is characterized by cystic spaces within a hypertrophied wall without enhancement. Adenomyomatosis can be identified by the "cotton ball sign", as described by Zatonski et al. [37]. When contrast-enhanced CT is performed, the cotton ball sign consists of fuzzy, gray enhancing dots in a thickened gallbladder wall or dots along the inner border of the gallbladder wall. About 25% of cases do not show the cotton ball sign due to Rokitansky-Aschoff sinuses filled with biliary sludge or calculus [37]. As a result, it can be difficult to distinguish benign adenomyomatosis from malignancy on CT, so early cholecystectomy should be considered if there is clinical suspicion of malignancy.

MRI

A "pearl necklace sign" on T2 weighted MRI images describes cystic spaces within thickened gallbladder wall that are intense at T2. Sinuses with biliary sludge or calculi or small (3 mm) may not exhibit the pearl necklace sign. Pearl necklace sign sensitivity, specificity, and accuracy on MRCP are 62%, 92%, and 74%, respectively. Mucin-producing gallbladder cancer, on the other hand, is a rare disease with high T1 and T2 signals within small cystic spaces that resembles adenomyosis in appearance. There is a much higher prevalence of adenomyomatosis than mucin-producing gallbladder cancer, and it needs to be treated as such.

CEUS

TAUS can be supplemented with CEUS if the equipment and expertise are available. On CEUS, adenomyomatosis is characterized by small, non-enhancing, avascular intramural foci on a background of thickened gallbladder walls. Malignancy is associated with serosal discontinuity, not intact serosa in adenomyomatosis [2].

HRUS

In addition to adenomyomatosis, HRUS is also useful for separating early gallbladder cancer from adenomyoma-

tosis. One small retrospective study in a single center found symmetrical wall thickening, cystic spaces within the walls, echogenic foci within the walls, as well as twinkling artefacts associated with adenomyomatosis. The loss of multilayer pattern in the gallbladder wall and intralesional vascularity were associated with cancer.

EUS

As with TAUS, EUS demonstrates similar findings in adenomyomatosis, but with a higher sensitivity. Adenomyomatosis investigations should not routinely use EUS due to its invasive nature and high cost [38].

PET

In uncomplicated adenomyomatosis, F-FDG PET shows no activity. In addition, localised uptake of FDG may be caused by chronic inflammatory changes.

Management

The management of adenomyomatosis is not governed by any national or international guidelines. Uncomplicated cases of adenomyomatosis are generally not followed up and not treated. It may be beneficial to obtain further imaging in cases where the diagnosis is unclear [39]. Symptomatic cases, unclear diagnoses, and malignant cases may benefit from cholecystectomy.

Conclusion

As a consequence of gallbladder injury, polyps and adenomyomatosis are commonly found in the gallbladder. Having a thorough knowledge of their appearance, natural history, and management is essential for radiologists. A review of multimodality imaging features has been conducted for both entities. In addition to TAUS, MRI is increasingly used to image the gallbladder and the biliary tree to diagnose and monitor these diseases. HRUS and CEUS, advances in ultrasound technology, may be used in specialist centres with sufficient expertise as adjuncts to TAUS. The imaging characteristics of each pathology may be similar, but there can also be overlaps with malignancy requiring early cholecystectomy.

Acknowledgments

None.

Conflicts of Interest

None.

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